We are currently investigating whether the effects of PIP_2 lipids are dependent on the phosphate group position, ionic strength, and temperature. Since the relative position of the hydrogen bond acceptor in phosphates are determined by their exact molecular structure, our results will be relevant in the context of molecular recognition involving PIP_2 lipids.

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Phospholipid Giant Unilamellar Vesicles (GUVS) Melt Like Large (LUVS), Not Mulitilamellar (MLVS), Vesicles

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The disparity between the excess heat capacity curves for the melting of large unilamellar vesicles (LUVs) and multilamellar vesicles (MLVs) has given rise to two hypotheses. The first is that the size of the vesicles results in a difference for how the two types of vesicles undergo their phase transitions. The second is that there is communication between the bilayers in an MLV when it transitions from its ordered gel phase to its liquid disordered phase, resulting in increased cooperativity. To test these hypotheses, differential scanning calorimetry (DSC) was performed on giant unilamellar vesicles (GUVs) of pure DPPC. The GUVs were prepared using electroformation, and visualized with confocal fluorescence microscopy. The average size of the GUVs determined from the images was about 7 micrometers. For comparison, the size of LUVs is about 100 nm. DSC was then performed of the GUVs, and their excess heat capacity curve was recorded. The excess heat capacity curves for the GUVs closely resemble the curves for LUVs. Both GUV and LUV curves are much broader (halfwidth ~ 1°C) than those of MLV curves (halfwidth ~ 0.1°C). The similarity of the GUV and LUV excess heat capacity curves indicate that the size of the vesicles does not impact how they undergo their phase transitions. In addition, the results provide evidence that there is cooperativity between the bilayers of an MLV when it undergoes its melting phase transition.

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Biomolecules Altering the Lipid Molecular Shape in Model Non-Lamellar Membranes

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Intracellular membranes exhibit complex, highly dynamic and non-lamellar morphologies.[1] Structural resemblance of such membranes with bicontinuous cubic and hexagonal lipid phases has been recognised in past two decades.[2] However, principles behind their dynamic organization and structural roles in cellular processes still remain elusive. Model membrane systems like liposomes, planar lipid bilayers and micelles have been largely used to interact various biomolecules to determine structures and functions of biomembrane systems.[3] However, these models are too simple to mimic complex intracellular membranes. Non-lamellar lipid self-assemblies exhibit some fundamental features that can be crucial while mimicking convoluted biomembrane architectures like, for example, continuous bilayer and aqueous networks of bicontinuous phases. Here we employed a model lipid-monoolein (MO) to form non-lamellar phases.[4] It is an unsaturated monoglyceride with C-18 chain. The average molecular shape is inverse conical (typical for majority of lipids), which is usually described by a 'shape factor', also called 'critical packing parameter' (>1 for inverse phases). By synchrotron small angle x-ray scattering we investigated changes in MO (Pn3m cubic) phase due to addition of a range of biomolecules (four different lipids, a protein, a sugar, a surfactant and three different oils). We further calculated molecular shapes and found that despite of variable sizes of lattice parameters the shape factor values stay within particular ranges. Each additive molecules studied here affects the molecular shape differently which helped us to understand their structural roles in non-lamellar biomembrane architectures.

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Does the Meyer-Overton Correlation Need to be Modified

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The linear relationship between the partition coefficient and anaesthetic potency is known as Meyer-Overton correlation. The homologous series of n-alcanols, upon elongation, shows increasing anaesthetic potency accompanied by an increase of the partition coefficient. However, the anaesthetic potency drops at a certain chain length although the partition coefficient still increases. This is known as cut-off effect. Although the cut-off effect is seemingly contradicting the Meyer-Overton correlation, we would like to show that the universal validity of the Meyer-Overton correlation still applies.
Instead of anaesthetic potency, the cut-off effect can also be described by the melting transition temperature of lipids. Recently, we have provided a thermodynamic theory to describe the principle of the freezing point depression, i.e. the anaesthetic solves better in the fluid phase of the membrane than the gel phase. Similarly, it has been shown that the longer n-alcanols cause an increase in the transition temperature. This indicates that these non-anaesthetic n-alcanols solve better in the gel phase of the membrane than the fluid phase, and we, therefore, suggest to extend the Meyer-Overton correlation to differentiate between solubility in the membrane and solubility in the fluid phase of the membrane.

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Association of Model Neurotransmitters with Lipid Bilayer Membranes

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The conventional model of synaptic transmission between neurons is based on the specific binding of neurotransmitters to ligand-gated ion channels. Fast perfusion electrophysiological studies of receptor responses to neurotransmitters have revealed complex kinetic behavior that cannot be reproduced unless the standard kinetic model is expanded to include additional conformational states. However, if one invokes neurotransmitter adsorption to the lipid membrane, the electrophysiological data can be reproduced with a simpler kinetic model that includes only the standard set of three conformational states [1]. This indirect mechanism of influence of neurotransmitters on receptor conformational transitions is assumed to be nonspecific. Unlike anesthetics, experimental verification has been difficult because of the low binding affinities of neurotransmitters to lipid bilayers [2]. We quantify this interaction by measuring the equilibrium dissociation constant of neurotransmitters on membranes with surface plasmon resonance (SPR) spectroscopy and characterize neurotransmitter association with bilayers through neutron reflectometry (NR) on artificial membranes. Sparsely-tethered bilayer lipid membranes (stBLMs) composed of zwitterionic (PC) and anionic (PS and PG) lipids were assembled and their interactions with serotonin and γ-aminobutyric acid (GABA) were studied as model systems. SPR shows a range of binding affinities for different neurotransmitters. Consistent with these results, NR shows that the ligand with the largest affinity (serotonin) penetrates the membrane deeply whereas GABA, for which the affinity is a tenth of serotonin, associates with the bilayer peripherally. Overall, we establish that some neurotransmitters interact non-specifically with the lipidic membrane matrix at physiologically relevant concentrations and that this interaction differs vastly for different neurotransmitters. These results could have a significant impact on our understanding of the molecular mechanism of synaptic transmission.

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Effects of Archaeal Tetraether Lipids on Membrane Partitioning of the Antifungal Drug Nystatin

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Nystatin is a polyene antibiotic that is frequently used in the treatment of cutaneous, vaginal, and oral fungal infections. It interacts with ergosterol in the fungal cell plasma membrane, causing membrane disruption and leakage, and leading to cell death. Liposomal nystatin has good antifungal activity but with significantly less systemic toxicity compared to free nystatin. In this study, we attempt to use archaeal tetraether lipids to increase the stability and drug loading of liposomal nystatin. Using a fluorometric method, we have determined the partition coefficient of nystatin into liposomes composed of cholesterol and POPC (80 mol%) in the absence and presence of archaeal tetraether lipids. We found that nystatin partition into liposomes increases significantly (by a factor of ~4-10) with the addition of 0.5 mol% archaeal tetraether lipids PLFE to replace 0.5 mol% cholesterol. PLFE is the polar lipid fraction E isolated from the thermoacidophilic archaeon Sulfolobus acidocaldarius. This dramatic change in nystatin partitioning engendered by PLFE was surprising and may result from the presence of interfacial regions between diester and tetraether lipid domains. This result plus our previous findings in PLFE-enhanced membrane stability suggest that tetraether lipids can be a useful additional component in liposomal nystatin formulations.